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Brief report

Differential outcome of bipolar patients receiving antidepressant monotherapy versus combination with an antimanic drug

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ABSTRACT

Introduction: Despite antidepressants are widely used in treating bipolar depression, there is much debate about their utility and their potential dangers, involving mood switches and suicidality. Our hypothesis was that the pattern of initial antidepressant prescription, i.e., alone (AM) or in combination with stabilizers (AC) might impact the long-term outcome of patients with bipolar disorder (BP). We aimed to test this hypothesis and to identify outcome measures that could be predicted by initial AM or AC treatment in patients with BP.
Methods: We included 95 patients with DSM-IV BP from a pool of 138 patients following a BP program. Patients were rated for initial AM vs. AC treatment when they were first seen in primary care and subdivided into two groups accordingly. Differences in their clinical course were sought investigating course both retrospectively and prospectively (mean follow-up 10 years). Primary outcome measures comprised suicidality and switch rate.
Results: There were significantly more patients who switched in the AM group than in the AC group. The number of suicide attempts was higher in the AM group. Significance was retained after performing logistic regression.
Limitations: Sample size was small and severe BP patients might be overrepresented in this sample.
Discussion: Initial AM treatment of patients subsequently diagnosed as BP may entrain a course characterized by higher proneness to switch and suicidal behaviour. Accurate initial diagnosis of bipolar depression should prompt combined treatment with antimanic drugs.

1. Introduction

Antidepressants (ADs) are the most prescribed drugs for depressive episodes of bipolar disorder (BP) (Baldessarini et al., 2007). These are used by psychiatrists and primary care physicians who often overlook that bipolar disorder could underlie a depressive episode (Baldessarini et al, 2010a), which frequently leads to AD prescription as mono-therapy, a practice that may not protect from manic/mixed switch or relapse, rapid cycling, and suicidal behavior (Altshuler et al., 2006; Vieta, 2008).

Since correct handling of drug treatment may impact the long-term course of bipolar disorder, in particular, mood stabilizer inclusion (Ågren and Backlund, 2007), and since AD administration may subtly affect the course of patients with BP (Born et al., 2009), we aimed to investigate two AD utilization patterns in a sample of patients with BP at their first depressive episode, one involving the administration of an AD combined with at least one mood stabilizer, the other consisting in the administration of one AD only.

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2. Methods

2.1. Study design and participants

From a pool of 138 patients with BP seen in primary care and other psychiatric centres subsequently referred to the Bipolar Disorders Program of the Hospital Clínic and University of Barcelona, we included patients who had received their *first* antidepressant treatment during a major depressive episode at the primary care setting, either as monotherapy (AM) or combined with a mood stabilizer(s) (AC) (N = 95). Each patient was classified as AM or AC depending on their first antidepressant regimen, independently from any change in treatment after entering our program. Other inclusion criteria comprised DSM-IV diagnosis of Bipolar type I (BP-I) or II (BP-II) Disorder, and providing written informed consent. The study was approved by the Ethics and Research Board of the Hospital Clínic. Patients were eligible for inclusion in this study if they satisfied the above criteria, thus they could differ both retrospectively and prospectively, as they were followed-up for different time intervals.

Clinical and demographic information was obtained from structured interviews with patients and their relatives using DSM-IV criteria for variables such as rapid cycling and seasonality We also collected data on social and occupational functioning and illness onset-related life events. Measures for data collection are part of the Barcelona Bipolar Disorders Programme Protocols (Vieta, in press).

2.2. Procedures and outcomes

To confirm diagnosis, we used both Structured Clinical Interview for DSM-IV (SCID) Axis I (SCID-I) (First et al., 1997a) and Axis II (SCID-II) (First et al., 1997b). We used a structured interview with the patient and/or relatives, as appropriate, to collect sociodemographic, clinical and drug treatment data. The 17-item Hamilton Depression Rating Scale (HDRS17) and the Young Mania Rating Scale (YMRS) were administered by trained raters to assess depressive and manic symptoms, respectively (Bobes et al., 2003; Colom et al., 2002), at least every three months.

To define specific course and outcome indicators during lifetime treatment with antidepressants, we chose operational definitions of symptomatic response, symptomatic remission, recovery, subsyndromal depression, relapse, recurrence and treatment-emergent mood switch almost identical to those developed by a Task Force of the International Society for Bipolar Disorders (ISBD) (Tohen et al., 2009).

Depressive predominant polarity (DPP) was diagnosed if at least two-thirds of the patient's past manic, hypomanic and depressive episodes were DSM-IV Major Depressive Episodes (Colom et al., 2006).

We compared the AC and AM groups for all measures shown in Tables 1 and 2. Suicidality was measured through the number of attempts since the beginning of drug treatment and based on the presence or absence of suicidal ideation (through the suicide item of the HDRS or specific questions during interview).

We set as primary outcome measures suicide-related measures, such as suicidal thinking and suicide attempts, and switch-related measures (percent patients switching and total number of switches) because of their high clinical and social importance.

2.3. Statistical analysis

We used the Statistical Package for Social Sciences (SPSS v.16 for Windows) for statistical analysis. AM and AC groups were compared for clinical and socio-demographic characteristics through Student's *t test* for continuous variables and the Chi-square test (χ^2) for discrete variables, as appropriate. Parametric tests were used according to sample distribution. For measures with few counts and non-normal distribution, like the number of suicide attempts, post-partum mood episodes, depressive and mood episodes, and hospitalizations, we used the Mann-Whitney *U*-test. All *p* values were two-tailed and statistical significance was set at $p<0.05$.

To control for the validity of our findings, we performed logistic regression using a backward stepwise model by assuming the initial ADs monotherapy (yes/no) as the dependent variable. We included as independent factors those variables which showed a statistical significance in univariate analyses and with a high clinical relevance with respect to our dependent variable: BP type, type of first episode, psychotic symptoms at first episode, current and past psychotic symptoms past switches with ADs and number of suicide attempts.

3. Results

3.1. Sample characteristics

Among the 95 BP-I and BP-II patients included in the final sample, 61 (64.2%) had taken the first AD as monotherapy (AM), while 34 (35.8%) took it in combination with mood stabilizers (AC). The first antidepressant was introduced on average at the second depressive phase (mean, 2.1; SD, 2.4). The mean number of antidepressants during the course of illness was 3.7 (SD, 2.3) and the mean duration of antidepressant treatment was 10.8 months (SD, 13.4). Mean duration of follow-up was 10.3 years (SD, 4.968).

AM and AC groups were comparable in terms of education, job qualification, working status and autonomy.

Demographic and clinical continuous and categorical (discrete) measures of the two groups are shown in Tables 1 and 2.

3.2. Outcomes

The *t*-test for equality of means showed significantly more suicide attempts in the AM group compared to AC and a lower ordinal number of the depressive episode at which the AD was first introduced in the AM group, meaning that AC received their first AD later (Table 2). AM patients were correctly diagnosed with BP later than AC ($p = 0.02$) and had more suicide attempts than AC ($p = 0.001$). After logistic regression, the significance of the higher switch rate ($\beta = 2.411$; Wald = 7.911; $p = 0.005$) and the higher number of suicide attempts ($\beta = 2.328$; Wald = 4.195; $p = 0.041$) in the AM group persisted. There were no significant differences between the two groups regarding years of illness, number of episodes (depressive, (hypo)-manic or mixed), number of